IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Sabine FRICKE et al.

Group Art Unit: 1617

Serial No.: 10/798,780 :

Examiner: San Ming HUI

Filed: March 12, 2004 :

For: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR RELIABLE ACHIEVEMENT OF ACCEPTABLE SERUM TESTERONE LEVELS

SECOND DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Sabine Fricke, being duly warned, declare that:

I am a citizen of Germany, residing in Jena, Germany.

I am an inventor of the above-captioned application.

If a patent issues from this application and if it is decided by the assignee to pursue a commercial product falling under its claims and if such a commercial product is approved by FDA and sold in the US, then under German law, I and the other inventors will receive some income derived from such sales.

I previously submitted two Declarations under 37 C.F.R. §1.132 previously in this application. My expertise for making this declaration is further demonstrated in the CV attached to the first of those two previous declarations that was signed by me on January 15, 2008.

I am familiar with the invention described in the above-captioned application and with

the grounds for rejection made against the claims of the application in the Office Action mailed June 12, 2009, from the U.S. Patent and Trademark Office. I have reviewed in detail the Riffkin et al. [J. Pharm. Sci. 53, 891-895 (1964)] reference cited in the Office action.

In the article, Riffkin et al. describe the parenteral administration of steroid hormones in highly-concentrated oily solutions, including in castor oil. In animal studies (Table III), an extended dwell time of oil in the muscle can be expected with a reduced number of injections.

Table IV in Riffkin et al. describes specific mixtures of their oily solution vehicles and Tables V and VI describe mixtures of certain steroids (not including testosterone undecanoate) with the vehicles. In the tables, Riffkin et al. describes the dependency of the lesion size on the rat muscle after the injection of mixtures of various oils with benzyl benzoate (and benzyl alcohol). The mixtures are described giving a % value for the oil and benzyl benzoate. However, no information on the type of percent (i.e., percent by volume or by weight) is provided by the authors, so that in principle, it remains open whether percent by volume or percent by weight is meant.

In practice, however, one skilled in the art will always meter pure castor oil by weight and not by volume. Because of its very high viscosity of 1000 mPa (by comparison, water has a viscosity of 1 mPa), castor oil would always, when metered by volume, continue to flow for a long time in a volume measuring device and would thus make it very difficult to ensure exact metering by volume.

Also, in a metering, e.g., by means of a scaled syringe, an exact volume metering would not be possible, since castor oil remains suspended in, among other places, the Luer cone of the syringe. The syringe thus would have to be back-weighted at the end to determine exactly the

amount that is actually dispensed.

In addition, the influence of the temperature plays a significant role in a volume metering. Before the production of the mixture, one skilled in the art would thus have to temper the individual components (castor oil and benzyl benzoate) to perform an accurate volume metering. In the case of castor oil, this would take a longer time because of the high viscosity. Advantageously, moreover, the process must be performed in an air-conditioned room. In any case, the amount of time and effort that would be needed to produce the mixture based on volume would be many times higher in comparison to that based on weight.

Another indication that percent by weight is meant comes from the statement (page 894, first paragraph):

> The addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favourable viscosity, making it easier to inject.

It would be counterintuitive to one skilled in the art – knowing the high viscosity of pure castor oil and the associated poor injectability – that metering would be conducted by volume for a volume% value of castor oil or mixture that consists of castor oil and benzyl benzoate.

In summary, it can be noted that because of the greater expenditure of time, the possibility for inaccuracy and the injection issues, one skilled in the art would not consider a metering by volume of castor oil. In view thereof, the only practical interpretation of the Riffkin et al. disclosure is that the % values given in the Tables refer to the percent by weight.

Although for the above reasons it is clear to me that Riffkin must refer to weight% for its values, I have conducted a further experiment to provide a comparison to Riffkin's 50% castor

oil/50% benzyl benzoate vehicle-only embodiment (Table IV), if it is assumed the values it discloses are in volume %. The experiment was conducted on this mixture under the same protocol as described in my previous declaration. The mixture is characterized as follows:

Mixing ratio:

25 g TU in a mixture of 53.9 weight% benzyl benzoate + 46.1 weight% refined castor oil

Conversion:

Based on a density for benzyl benzoate of 1.12 g/cm^3 and a density for refined castor oil of 0.958 g/cm^3, this mixture converts to the following volume % values:

25 g TU in a mixture of 50 vol% benzyl benzoate + 50 vol% refined castor oil

Results:

Stability of the oily solutions at 2-8 °C (fridge) The solutions were considered stable if there was exhibited no precipitate (crystals) in the ampoule after 34 days time. The data are shown in the attached table. The only solution which maintained sufficient solubility in the tests was a solution containing TU in a 37 weight% (40.7 vol%) castor oil and 63 weight% (59.3 vol%) cosolvent oily solution.

The data, as follows, are presented in the same format and together with the castor oil data from my previous declaration. The new data is in the bold-type row. The last row corresponds to the claimed invention.

Formulations containing refined castor oil for parenteral use	***Number of ampoules with precipitation (crystals) at 2-8 °C after***								
	0 d	**1 d**	**2 d**	**3 d**	**6 d**	**8 d**	**10 d**	**21 d**	**34 d**
40 weight% benzylbenzoate	0	5	6	6	6	6	6	6	6
50 weight% benzylbenzoate	0	0	1	3	3	3	3	4	5
53.9 weight% benzylbenzoate	**0**	**0**	**2**	**2**	**3**	**6**	**8**	**8**	**8**
63 weight% benzylbenzoate	0	0	0	0	0	0	0	0	0

The additional data are consistent with my previous declaration demonstrating that castor oil is surprisingly advantageous when used in a lower concentration relative to the cosolvent according to the claimed invention – even when compared to a 50 vol%/50 vol% castor oil/benzyl benzoate vehicle.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

26.08.2009
Date

Dr. Sabine Fricke